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CASE REPORT

Treatment of six cases of equine corneal stromal abscessation with intracorneal injection of 5% voriconazole solution

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Abstract

Objective To describe a reproducible technique for intrastromal injection in the standing horse for treatment of corneal stromal abscessation.

Animal Studied A retrospective clinical study addressing the history, treatment, and outcome of six equids (six eyes) that received intrastromal voriconazole injection.

Procedure Equids having a deep stromal abscess suspected to be of fungal origin were administered intrastromal injection of 5% voriconazole solution under standing sedation in an effort to bring about enhanced resolution of clinical disease.

Results Intracorneal administration of 5% voriconazole solution resulted in resolution of clinical disease, specifically stromal abscessation and secondary uveitis. All animals displayed decreased blepharospasm and no significant complications in the immediate postinjection period. Convalescent periods were subjectively shorter than anticipated with traditional medical therapy. All animals developed mild to moderate stromal fibrosis relative to the initial severity and depth of abscessation.

Conclusions Intrastromal injection of 5% voriconazole solution may provide a safe and effective treatment option for corneal stromal abscessation in horses. In all reported cases, administration of injection early in the treatment period appeared to contribute to rapid resolution of clinical disease without significant complications. The authors present this technique as an alternative to traditional surgical intervention, being more economical, having shorter treatment duration, and potentially resulting in less scar formation.

Key Words: abscess, cornea, equine, intracorneal, stroma, voriconazole

INTRODUCTION

Corneal disease in horses occurs frequently and is often believed to be the result of trauma, allowing for bacterial or fungal infection.[1] Horses are considered predisposed to ulcerative keratitis due to eye position, disposition, husbandry, and degree of exposure to environmental microbes.[2] Infectious keratitis, particularly stromal abscessation, is a painful condition and can pose a significant threat to vision.[3] Disruption of the corneal epithelium allows exposure of commensal or environmental microbes to the underlying stroma.[4,5] During re-epithelialization of the ulcer, these microbes can become trapped within the stroma, resulting in abscess formation.[3,6,7] Moreover, the epithelium also serves as a barrier to protect the trapped fungi or bacteria from topical medications.[8]

Stromal abscesses were previously thought to be bacterial in origin, however, it is now known that fungus is frequently involved.[1,4,6,7,9] In fact, current literature indicates that fungus plays a critical role in deep stromal abscess formation due to its affinity for the posterior stroma and Descemet's membrane.[3,9] *Aspergillus* and *Fusarium* spp. are the most common fungal isolates encountered in equine keratomycosis in the United States, with *Candida* spp. also commonly isolated in the northeast.[5,10] The effectiveness of topical antifungal agents depends on the associated spectrum of activity and ability to achieve adequate corneal and aqueous concentrations.[11] Topical antifungal medications are often required to be applied as frequently as every 4 h, and the treatment period may last for weeks or months postinfection.[8] Prognosis for vision and retention of the globe is often dependent on aggressive and

accurate initial therapy. Prolonged treatment with expensive medications contributes to the high cost of managing this disease.[6] When combined with hospitalization due to owner inability to provide frequent medication administration, treatment cost can be considerable. Moreover, the incidence of stromal abscessation in horses has increased in recent years, presenting a need for more effective, economic treatment options.[3,6] Combination of medical and surgical therapy has been recommended for improved outcome in stromal abscess cases. In particular, more anteriorly located stromal abscesses are more likely to be bacterial in origin and respond to medical therapy, while those abscesses that are thicker or deep within the stroma heal more quickly with surgical intervention.[8] Surgical options include penetrating keratoplasty and targeted lamellar keratoplasty, with or without conjunctival or amnion graft placement. With surgical intervention, the main concern is graft rejection and resultant corneal scar formation, which can affect vision.[12]

Recently, intrastromal injection of antimicrobials has been reported for treatment of stromal abscesses in humans and horses that failed to respond to traditional medical therapy. Injection resulted in early and complete resolution of disease.[13–20] Few reports exist concerning intrastromal injection in horses, with an obvious lack of standardized technique.[13,19] This case series details a technique used for intrastromal injection in five horses and 1 mule as treatment for stromal abscessation.

CASE REPORTS

History and signalment

Records were reviewed for all equids receiving intrastromal corneal injection at Oklahoma State University Veterinary Teaching Hospital (OSU VTH) during a 6-month period. The identified population included five horses and 1 mule. Breeds included Quarter Horse (2), Arabian (1), Warmblood (1), and Paint Horse (1). There were three mares and three geldings aging from 4 to 22 years (mean 9.2 years). Initially, all six animals were reported by their owners to have displayed blepharospasm and epiphora, with or without a cloudy-appearing cornea. All cases had been evaluated by a veterinarian prior to presentation and were receiving a variety of treatments (Table 1). Three horses received antifungal treatment for 5–8 days prior to referral. Four horses were referred specifically for treatment of a stromal abscess, whereas the remaining two animals had stromal abscesses detected by the OSU VTH ophthalmology service. Three horses had subpalpebral lavage (SPL) systems in place prior to referral. The average duration of treatment prior to referral was 15 days. Case 5 had only received systemic treatment prior to referral and no topical ophthalmic medications.

Ophthalmic examination findings

On presentation, all animals received a full ophthalmic examination including slit-lamp biomicroscopy (Kowa SL-14; Kowa Co., Tokyo, Japan) and fluorescein staining. In most cases, corneal pathology, uveitis, and/or the presence of posterior synechiae precluded visualization of the fundus in the affected eye. All cases had a solitary corneal opacity in one eye that ranged in size from 2 to 5 mm. One opacity extended from mid to deep stroma, while all other opacities were in the deep stroma (Table 2). The right eye was affected in two cases, while the left was affected in four cases. In cases 1, 3, 4, and 5, a cellular infiltrate was present in the anterior chamber adhered to the endothelium subjacent to the abscess. Fluorescein stain

Table 1. Therapy administered to the six cases of equine corneal stromal abscessation prior to presentation to the Oklahoma State University Ophthalmology Service

Case	Signalment	Eye affected	SPL placed	Topical ocular treatment	NSAID therapy	Length of treatment
1	13 y.o. Quarter Horse mare	Right	Yes	Ciprofloxacin q4h Miconazole 1% q6h Atropine 1% q12h	FM	1 week
2	4 y.o. Oldenburg mare	Left	No	Neomycin/Polymixin/ Bacitracin q8h Atropine 1% q12h	None	6 weeks, intermittent
3	5 y.o. Paint gelding	Left	Yes	Ciprofloxacin q6h Miconazole q6h Serum q6h Atropine 1% q24h	FM	8 days
4	4 y.o. Quarter Horse gelding	Right	Yes	Atropine 1% q24h Ciprofloxacin q6h Miconazole q6h*	FM	26 days
5	7 y.o. Mule gelding	Left	No	None	PB	6 days
6	22 y.o. Arabian mare	Left	No	Ciprofloxacin q8h Flurbiprofen q8h	None	4 days

SPL = subpalpebral lavage, NSAID = nonsteroidal anti-inflammatory drug, FM = flunixin meglumine, PB = phenylbutazone, y.o. = years old.
*Used for 5 days prior to presentation.

Table 2. Corneal abscess description and level of associated uveitis at the time of presentation as well as treatment duration in the six equine cases treated with intracorneal 5% voriconazole solution

Case	Abscess location	Abscess size	Abscess depth	Corneal vascularization	Level of uveitis	Time until treatment cessation
1	12 o'clock, paracentral	5 mm	Deep stroma	Circumferential, 3–4 mm, anterior to abscess	Mild	7 weeks
2	6 o'clock, perilimbal	2 mm	Deep stroma	Few, thin vessels extending anterior to abscess	Mild	5 weeks
3	9 o'clock, paracentral	4 mm	Deep stroma	Circumferential, 6–7 mm, anterior to and invading abscess	Moderate	4 weeks
4	9 o'clock, paracentral	5 mm	Deep stroma	Circumferential, 6–7 mm, anterior to abscess	Moderate	7 weeks
5	7 o'clock, paracentral	5 mm	Deep stroma	Circumferential, 4 mm	Severe	4 weeks
6	6 o'clock, perilimbal	4 mm	Mid to deep stroma	Circumferential, 4 mm, anterior to abscess	Mild	6 weeks

uptake was negative in all cases. All animals had some degree of corneal vascularization ranging from case 3 with vessels invading the abscess to case 2 with few, small vessels present. The degree of uveitis present was largely dependent upon previous treatment, as most animals were presented on atropine and/or systemic nonsteroidal anti-inflammatory drug (NSAID) therapy. Mild cases of uveitis displayed localized corneal edema, miosis, and trace flare. Moderate uveitis was characterized by the previous signs as well as iritis, fibrin in the anterior chamber, and/or 1–2/4+ aqueous flare (Fig. 1). Case 5 had severe uveitis, characterized by diffuse, 3/4+ corneal edema, hypopyon, fibrin in the anterior chamber, and profound miosis (Fig. 2). This animal had received no topical ophthalmic therapy prior to presentation.

Intracorneal injection

In all cases, a 5% voriconazole solution was aseptically prepared just prior to the procedure. One 200-mg vial of injectable voriconazole (Vfend I.V., Pfizer Pharmaceuticals, New York, NY, USA) lyophilized powder was reconstituted using 3.5 mL of sterile water to obtain 4 mL of clear solution containing 50 mg/mL of drug. Vigorous agitation of the solution was required to complete the reconstitution. The solution was drawn up into a 1-mL tuberculin syringe and transferred in 0.2 mL aliquots to three separate 3-mL Luer-lock syringes. A 27 gauge needle was then attached to each syringe and bent at a 30–45 degree angle near the hub. The procedure was performed using heavy standing sedation, specifically intravenous detomidine 0.015 mg/kg and butorphanol 0.01 mg/kg. Approximately 5 min after sedation administration, auriculopalpebral and supraorbital nerve blocks were performed for the affected eye, each using 1 mL of 2% lidocaine. The surface of the eye and adnexa were aseptically prepared using a 1:10 dilution of betadine solution. Subsequently, the corneal surface was desensitized by topical application of 0.5 mL of 2% lidocaine every 30 s for 5 min (5 mL total volume). A Castroviejo eyelid speculum was placed to provide corneal exposure and retract the third eyelid, and a 5–10X head loupe was

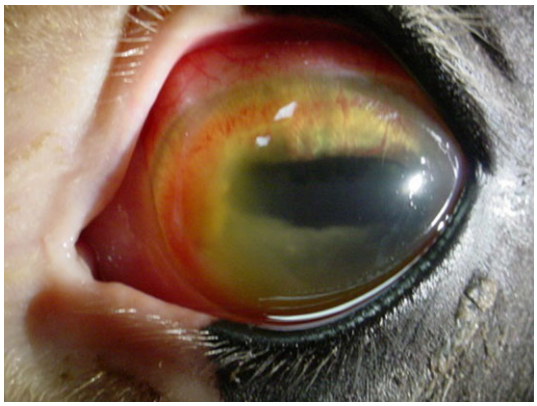

Figure 1. Case 3 on presentation displaying signs of moderate uveitis (miosis, iritis, fibrin in the anterior chamber, 1+ aqueous flare) secondary to a deep stromal abscess.

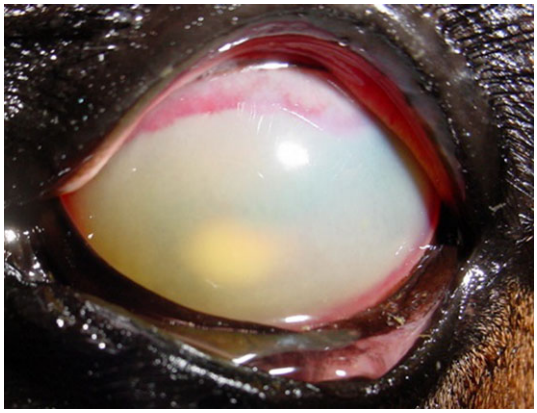

Figure 2. Case 5 on presentation displaying signs of severe uveitis (diffuse, 3/4+ corneal edema, hypopyon, fibrin in the anterior chamber, and profound miosis) obscuring full view of the deep stromal abscess.

worn for magnification. The needle was inserted nearly parallel to the corneal surface starting at a point 2–3 mm abaxial to the near side of the dorsal aspect of the lesion. The needle traversed horizontally along lamellar planes anterior to the abscess to stop just beyond the opposite extent of the lesion (Fig. 3). The voriconazole solution was then injected slowly as the needle was withdrawn. An additional two injections were administered in a similar manner, one across the center of the lesion and the other across the ventral aspect of the lesion. All doses were injected in the corneal stroma just anterior to the lesion, covering as much of the abscess bed as possible. The dosage and injection technique in this study were adapted from previous studies by Cutler, Tsujita, Sharma, and Tu.[13,17,19,20] A total of 22.5 mg of voriconazole was injected into the corneal stroma in each animal.

Following the procedure, a subpalpebral lavage system (Mila International Inc., Erlanger, KY, USA) was placed in the superior eyelid if one was not already present. Traditional medical therapy was prescribed concurrently, consisting of voriconazole 1% solution every 4 h, ofloxacin 0.3% every 4 h, and atropine 1% every 6–12 h (based on severity of uveitis). Cases 3 and 6 received topical ciprofloxacin instead of ofloxacin. Due to the presence of a vascularized abscess, case 3 received oral fluconazole at 14 mg/kg PO once followed by 5 mg/kg PO every 24 h for 9 days. Case 2 received a single dose of flunixin meglumine at 1 mg/kg IV following the procedure. This animal remained hospitalized for 3 days for monitoring and required no further NSAID therapy. The remaining cases received flunixin meglumine at 1 mg/kg PO or IV every 12+ h for at least 5 days. Therapy was tapered based on clinical improvement. Case 5 remained hospitalized for 9 days postinjection. The remaining cases were discharged into the owner's care immediately after the injection procedure. There were no immediate complications detected following the procedure in any animal.

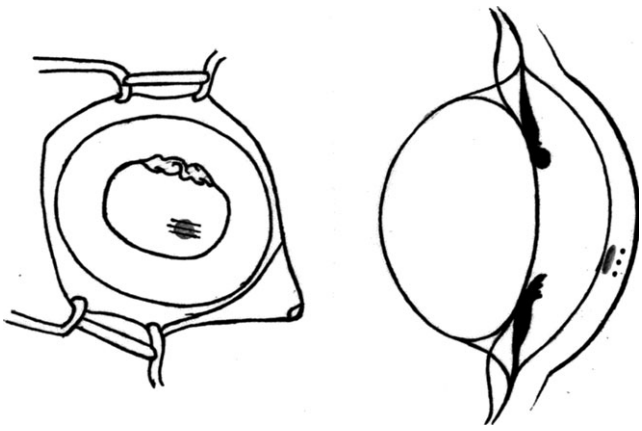

Figure 3. Image on the left illustrates a paracentral deep stromal abscess (gray circle) and the 3 parallel intracorneal injection tracts utilized (black lines). Note that the injections span just beyond the medial and lateral borders of the lesion, with the goal to infiltrate an area no smaller than the size of the abscess. The image to the right illustrates needle placement (three dots) in the stroma just anterior to the abscess (gray oval).

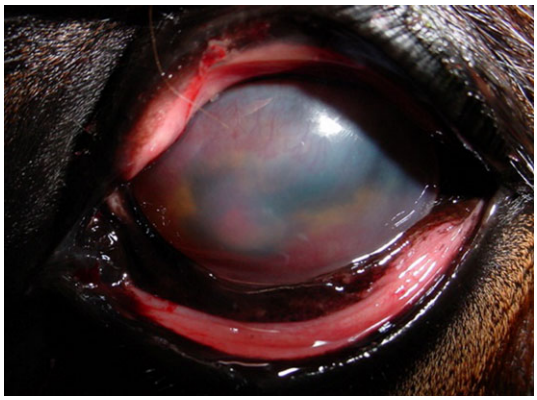

Figure 4. Case 5 upon discharge 10 days after undergoing intracorneal injection.

Clinical progression and outcome

By discharge, case 5 had shown profound corneal clearing, vessel attenuation, and uveitis control (Fig. 4). All other cases had recheck examinations approximately 2–3 weeks after injection. Typical findings included regression of corneal vascularization, resolution of cellular infiltrate in the abscess bed, and corneal fibrosis. A second recheck examination was performed between 2 and 4 weeks later. At that time, all treatments were discontinued, and the lavage system removed. All cases retained vision in the affected eye with mild to moderate stromal fibrosis in the previously abscessed region of the cornea. All cases also displayed mild, linear stromal fibrosis in parallel, horizontal lines, consistent with scarring of the needle tracts from injection (Fig. 5). Cases 4 and 5 retained the posterior synechiae noted at the time of initial examination. No corneal edema or endothelial changes were grossly noted in any case. No animal required more than 2 recheck examinations, with total convalescent periods from time of injection to cessation of treatment ranging from 4 to 7 weeks. At the time of publication, five of six cases were visual and comfortable in the affected eye with no relapse of disease or progression of corneal fibrosis (follow-up range: 2 weeks to 7 months). Case 3 was euthanized due to unrelated illness approximately 7 months after injection, but was visual and comfortable in the affected eye with no relapse of disease prior to euthanasia.

DISCUSSION

Keratomycosis is a relatively common disease in horses that can pose a significant threat to vision.[4,21] Medical therapy is considered a first-line treatment to control the

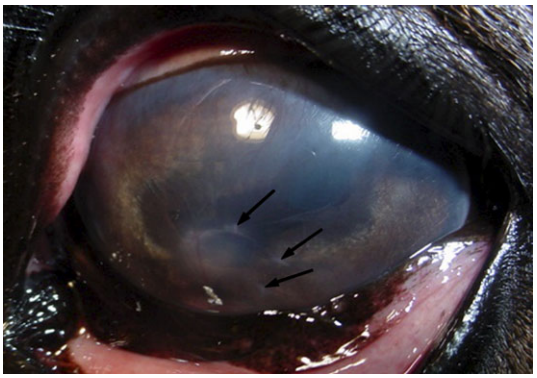

Figure 5. Case 5 at 4 weeks after intracorneal injection. Note the 3 thin horizontal lines of stromal fibrosis that have developed in the needle tracts (black arrows). All treatment was discontinued.

infection and secondary uveitis present in cases of stromal abscessation. Traditionally, treatment continues until the abscess has become vascularized and healed, often taking weeks to months and resulting in significant corneal fibrosis. Medical therapy is ideally directed by identification of inciting organisms. Stromal abscesses have an intact overlying epithelium that will impair one's ability to obtain samples for analysis. Therefore, histopathology and culture of keratectomy specimens may be the only way to obtain a definitive etiological diagnosis and institute proper antimicrobial therapy.[6] In some cases, clinical course, depth of abscessation, intensity of anterior uveitis, the presence of satellite lesions, time of year, and the geographic location of the animal may support the presumption of fungal involvement.[8,22,23] For the cases in this report, depth of abscessation, level of anterior uveitis, clinical course, and the commonality of fungal infection in Oklahoma supported treatment with voriconazole. Although samples are not routinely obtained from stromal abscesses, ulcerative fungal keratitis cases presenting to the OSU VTH almost always have cytologic or histologic characteristics consistent with *Aspergillus* or *Fusarium*. Similarly, in the cases in which fungal culture is performed, *Fusarium* or *Aspergillus* is most commonly isolated. Although fungal sensitivity testing is not performed on clinical cases, the best clinical response to therapy has been with miconazole 1% or voriconazole 1%. The latter is now the drug of choice based on the sensitivity pattern reported for the Midwest and southern United States.[10]

Several surgical techniques exist for treatment of stromal abscessation including penetrating keratoplasty, posterior lamellar keratoplasty, deep endothelial lamellar keratoplasty, and deep anterior lamellar keratoplasty, with or without placement of an overlying conjunctival or amnion graft.[4] With surgical intervention, the main concern is graft rejection and resultant corneal scar formation as well as the inherent risks of general anesthesia. Despite graft rejection and scar formation, the reported success rates for positive visual outcome range from 77.9 to 98.1% depending on the surgical technique used.[24] This is because the horse retains vision around the site of scar formation, provided there has not been extensive damage to the internal ocular structures from uveitis.[3]

The foundation of intrastromal injection stems from its use in human ophthalmology. Several case reports indicate clinical success of globe retention, however, the patients often had extremely limited vision in the affected eye due to resultant scar formation. Yet, in the absence of intracorneal injection, one could argue that lack of fungal control by traditional medical therapy would have led to globe rupture or severe scar formation on its own. To date, intracorneal injection has only been documented for use in humans and horses as a salvage procedure after patients fail to respond to traditional medical therapy.[13,15–17,19,20] In this report, cases 1, 3, and 4 had been on antifungal therapy (miconazole) for only 5–8 days prior to presentation, and the remaining cases had not received antifungal therapy. Thus, intracorneal injection was used as part of the initial treatment to increase drug levels within the cornea.

Although all cases had clinical resolution of disease, the exact mechanism of action, duration of drug effect, and interaction of intracorneal and topical medications are unknown. Use of the antifungal voriconazole was selected based on the clinical suspicion of fungal involvement. As is the case with most deep stromal abscesses, identification of the inciting organism, if any, is often impractical or impossible, leading to reliance on clinical appearance to dictate treatment. Several proposed benefits of intracorneal injection include achieving higher concentration of drug within the cornea, mechanical disruption and thinning of purulent debris allowing for improved clearance of material, and stimulation of the corneal immune defenses through the presence of a foreign substance and disruption of corneal architecture. All cases received concurrent traditional topical therapy, which likely contributed to resolution of disease. It is possible that topical treatment alone would have allowed for clinical resolution of disease without intracorneal injection. Further research is warranted to determine the mechanism by which intrastromal injection is effective as well as the duration of efficacy. Until that time, it is the authors' recommendation that this intracorneal injection procedure be used in conjunction with traditional broad-spectrum, topical therapy.

The dose of antifungal utilized in intrastromal injection must take into account three critical pieces of information: total quantity of fluid that can be safely injected into the cornea, the anticipated level at which the antifungal becomes toxic to the cornea, and the anticipated MIC for the fungus involved. The authors of this study empirically chose a concentration of 5% (50 mg/mL) voriconazole. Previous human studies have utilized a 0.05% (0.5 mg/mL) voriconazole solution with total volume injected at 0.1 mL (50 μg total dose).[15,17,18] The equine stroma is

three times as thick as human corneal stroma, which should allow for larger sized abscesses and retention of greater fluid volume.[1,25] In the case of voriconazole, corneal toxicity studies have not been performed in the horse. Two studies were recently published regarding the toxicity of voriconazole on human and rabbit corneal endothelial cells.[26,27] The *in vitro* human study indicated a dose-dependent voriconazole toxicity. Exposure of voriconazole at >100 μg/mL (0.01%) was toxic to human endothelial cell cultures; concentrations of ≤50 μg/mL (0.005%) resulted in no significant cell damage.[26] In contrast, intracameral voriconazole injection of up to 166.7 μg/mL (0.017%) showed no significant toxic effects on rabbit endothelium.[27] No studies have been published addressing the effect of voriconazole on other corneal cell lines. The concentration of voriconazole used intrastromally in this report is much greater than the toxic level reported in humans and rabbits. However, no grossly apparent toxic effects were noted to the cornea. This is similar to previous reports using a 1% (10 mg/mL) solution, also a much higher concentration than has been shown to be toxic in other species.[13,19] As variation in cellular tolerance to voriconazole has already been reported between species, further research is warranted to determine the toxic dose of voriconazole on equine corneal cells. A previous report demonstrated horses to have increased blepharospasm and other signs of irritation following topical application of 3% voriconazole.[11] This was not observed following intracorneal injection in any of the cases reported. The intraocular toxicity of voriconazole has not been assessed in the horse; however, retinal toxicity has been studied in rats following intravitreal injection, with no abnormalities detected using vitreal concentrations up to 25 μg/mL.[28] In other reports, intracorneal injection of 1% voriconazole solution resulted in rapid disease resolution and retention of vision in five horses.[13,19] No electroretinographic studies were performed on these horses, although fundic examination findings remained unchanged, and no visual deficits were detected. As for fungal MIC levels, there is no known way to consistently identify the fungus involved in a stromal abscess without culture or histopathologic analysis of corneal samples obtained upon surgical resection or debridement. Even then, histopathology will not allow identification to the species level, and MIC can vary greatly between species. In addition, MIC standardization does not yet exist in veterinary medicine, resulting in uncertainty over the clinical efficacy of a drug.

All cases responded rapidly to treatment and sustained subjectively shorter overall treatment periods than what would be anticipated with standard medical therapy, which has traditionally been a minimum of 8 weeks. Treatment periods reported here may have been shorter if the animals had been re-evaluated earlier, therefore, the convalescent periods reported may be conservatively long depending on owner scheduling and travel ability. Five of six cases were visual at the time of publication with no relapse of abscessation or uveitis. Case 3 was euthanized due to unrelated illness approximately 7 months after intracorneal injection, but was visual and comfortable in the affected eye with no relapse of disease prior to euthanasia. Although mild to moderate stromal fibrosis was detected in all cases, it was apparent that the affected cornea continued to remodel over time, resulting in a decrease in size and density of scars. For reasons unknown, it is a common finding that corneal vascularization infiltrates the stroma just anterior or posterior to the abscess but fails to invade it, and vascularization of the abscess itself is believed to be required for healing.[3,6,8] However, as seen in this study and others, intrastromal injection appears to attenuate vessels or allow the abscess to heal without vascularization.[13] It is possible that this vessel attenuation and subsequent sparing of stromal disruption is the mechanism for decreased scar formation.

The use of intracorneal injection in clinical cases must be considered carefully as the procedure is not without risk. Although the animals in this report had no significant complications, previous reports list corneal lamellar fracture, anterior stromal laceration, intracameral injection, and conjunctival hyperemia as possible immediate complications of the procedure.[13,19] In addition, in the case of nonsensitive organisms, it is possible to spread microbes within the needle tract or into the anterior chamber if the abscess itself is penetrated. This would potentially result in worsening of disease.[19] Regarding chronic complications, all cases developed linear stromal opacity consistent with scarring of the needle tracts, similar to other reports.[13,19] Due to the presence of concurrent uveitis, all intraocular changes such as posterior synechiae and cataract formation could not be attributed to the injection procedure itself. Subjectively, the equids in this study displayed stromal fibrosis that was less dense than anticipated with surgical or traditional medical therapy alone, given the size and severity of the abscess. Although all cases displayed linear fibrosis along the injection tracts, the impact on vision would be considered negligible. The present cases had varying levels of uveitis as well as a range of abscess size, location, vascularization, and stromal depth, but all responded equally well to one episode of intrastromal injection (Table 2).

This report demonstrates the relative safety and apparent efficacy of intrastromal injection of 5% voriconazole solution for treatment of deep stromal abscessation in horses. Further studies are needed to assess the toxicity of 5% voriconazole to the cornea as well as assess the effects of intrastromal injection on the normal equine eye. This case series may indicate that earlier injection may offer a therapeutic advantage in cases suspected to have fungal involvement. The authors present this technique as an alternative to surgical intervention, being more economical, avoiding the risks of anesthesia, having shorter treatment duration, and likely resulting in less scar formation.

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